Clinical trial results:
Study of Optimal Replacement of Thyroxine in the ElDerly (SORTED)
A Randomised Controlled Trial (Feasibility study)

Summary

EudraCT number	2011-004425-27
Trial protocol	GB
Global end of trial date	15 October 2014

Results information

Result version number	v1 (current)
This version publication date	11 August 2016
First version publication date	11 August 2016

Trial information

Trial identification

Sponsor protocol code	5863

Additional study identifiers

ISRCTN number	ISRCTN16043724
ClinicalTrials.gov id (NCT number)	NCT01647750
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Newcastle Upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Joint Research Office, Regent Point (Level 1), Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Dr Salman Razvi, Gateshead Health NHS Foundation Trust, 0044 1914456052, salman.razvi@ghnt.nhs.uk
Scientific contact	Dr Salman Razvi, Gateshead Health NHS Foundation Trust, 0044 1914456052, salman.razvi@ghnt.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2013
Global end of trial reached?	Yes
Global end of trial date	15 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were:
• To assess participant's willingness to enter the trial
• To gauge participant's acceptability of study design.
• To study length of time required to complete recruitment.
• To assess the dose titration strategy, described above, and length of time required to achieve desired TSH levels.
• To gauge medication compliance.

There was also a qualitative study and a retrospective cohort study combined in the protocol for this study.

Protection of trial subjects:

Blood samples may cause discomfort and/or bruising (this should be transient), or rarely infection. Venepuncture was routinely performed in these patient's to assess L-thyroxine dose.
Multiple questionnaires were required to furnish a larger RCT. The order of completion was carefully considered (as documented in the current protocol), such that the most important study information was gathered first prior to any patient fatigue.
The common side effects of under treatment of hypothyroidism are tiredness, increased awareness of the cold, difficulty in concentrating, dry skin and hair, and weight gain. If the dose of levothyroxine is too high, common symptoms may include diarrhoea, vomiting, chest pain, fast heart rate, insomnia, flushing, sweating, weight loss, palpitations and muscle weakness. Participants may be familiar with the side effects of LT4 they currently take (although brand may be different). We saw participants regularly and assessed their symptoms. Participants were provided with a telephone helpline number to ring in case of concern. They were also provided with a "patient alert card" containing emergency numbers if required.

Background therapy:

none

Evidence for comparator:

The IMP for the randomised controlled trial (RCT) is routinely used in patients with hypothyroidism.

Actual start date of recruitment	17 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	29
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

The trial opened for recruitment in the UK only on 17th October 2012 and the first patient was randomised on 9th November 2012. The trial closed to recruitment on 10th July 2013. 48 patients were randomised. The last patient to enter the study was randomised on 10th July 2013.

Pre-assignment

Screening details:

Subjects were screened via either GP practices using an eligibility proforma provided by the PCRN research team or via secondary care using a medical record review at routine clinics at Gateshead Health NHS Foundation Trust and the Newcastle upon Tyne Hospital NHS Foundation Trust. For detailed Inclusion/Exclusion criteria please refer to protocol.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Single-blind will be achieved by de-blistering and over-encapsulation, using a capsule filler of Lactose BP. For doses that are multiples of 50mcg, we will over-encapsulate Eltroxin/Levothyroxine 50 mcg tablets; for the remaining 25mcg, 75mcg and 125mcg dose increments, we will over-encapsulate Eltroxin/Levothyroxine 25mcg tablets. Capsules will be re-packaged into an appropriate bottle container (polypropylene) and labelled in accordance with Annex 13.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard dose

Arm description:

Participants will be randomised to usual dose LT4 (their current dose) to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group.

Arm type	Active comparator
Investigational medicinal product name	Levothyroxine
Investigational medicinal product code	
Other name	Eltroxin
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants will be randomised to usual dose LT4 (their current dose) or lower dose LT4 to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group. On the other hand, to achieve the desired target TSH levels for the lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1. IMP will be provided as two separate 13 week supplies of LT4 (dispensed separately at visits 1 and 2), packaged into appropriate individual bottles (polypropylene). The container will be labelled in accordance with Annex 13 but will not indicate details of the arm of the study the participants have been randomised to. The Annex 13 label will instead contain a pack number, which will be the link to relevant packaged dose.

Arm title	Reduced Dose

Arm description:

Participants will be randomised to lower dose LT4 to be taken once daily. For participants randomised to lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1.

Arm type	Experimental
Investigational medicinal product name	Levothyroxine
Investigational medicinal product code	
Other name	Eltroxin
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants will be randomised to usual dose LT4 (their current dose) or lower dose LT4 to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group. On the other hand, to achieve the desired target TSH levels for the lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1. IMP will be provided as two separate 13 week supplies of LT4 (dispensed separately at visits 1 and 2), packaged into appropriate individual bottles (polypropylene). The container will be labelled in accordance with Annex 13 but will not indicate details of the arm of the study the participants have been randomised to. The Annex 13 label will instead contain a pack number, which will be the link to relevant packaged dose.

Number of subjects in period 1	Standard dose	Reduced Dose
Started	24	24
Completed	24	24

Period 2

Period 2 title	Follow Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Single-blind will be achieved by de-blistering and over-encapsulation, using a capsule filler of Lactose BP. For doses that are multiples of 50mcg, we will over-encapsulate Eltroxin/Levothyroxine 50 mcg tablets; for the remaining 25mcg, 75mcg and 125mcg dose increments, we will over-encapsulate Eltroxin/Levothyroxine 25mcg tablets. Capsules will be re-packaged into an appropriate bottle container (polypropylene) and labelled in accordance with Annex 13.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Dose

Arm description:

Participants will be randomised to usual dose LT4 (their current dose) to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group.

Arm type	Active comparator

Investigational medicinal product name	Levothyroxine
Investigational medicinal product code	
Other name	Eltroxin
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants will be randomised to usual dose LT4 (their current dose) or lower dose LT4 to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group. On the other hand, to achieve the desired target TSH levels for the lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1. IMP will be provided as two separate 13 week supplies of LT4 (dispensed separately at visits 1 and 2), packaged into appropriate individual bottles (polypropylene). The container will be labelled in accordance with Annex 13 but will not indicate details of the arm of the study the participants have been randomised to. The Annex 13 label will instead contain a pack number, which will be the link to relevant packaged dose.

Arm title	Reduced Dose

Arm description:

Participants will be randomised to lower dose LT4 to be taken once daily. For participants randomised to the lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1.

Arm type	Experimental
Investigational medicinal product name	Levothyroxine
Investigational medicinal product code	
Other name	Eltroxin
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants will be randomised to usual dose LT4 (their current dose) or lower dose LT4 to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group. On the other hand, to achieve the desired target TSH levels for the lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1. IMP will be provided as two separate 13 week supplies of LT4 (dispensed separately at visits 1 and 2), packaged into appropriate individual bottles (polypropylene). The container will be labelled in accordance with Annex 13 but will not indicate details of the arm of the study the participants have been randomised to. The Annex 13 label will instead contain a pack number, which will be the link to relevant packaged dose.

Number of subjects in period 2	Standard Dose	Reduced Dose
Started	24	24
Completed	21	19
Not completed	3	5
Consent withdrawn by subject	3	5

Baseline characteristics

Reporting groups	
Reporting group title	Standard dose
Reporting group description:	
Participants will be randomised to usual dose LT4 (their current dose) to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group.	
Reporting group title	Reduced Dose
Reporting group description:	
Participants will be randomised to lower dose LT4 to be taken once daily. For participants randomised to lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1.	

Reporting group values	Standard dose	Reduced Dose	Total
Number of subjects	24	24	48
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	14	15	29
85 years and over	10	9	19
Age continuous			
Units: years			
median	83	82.5	
full range (min-max)	80 to 91	80 to 93	-
Gender categorical			
Units: Subjects			
Female	18	16	34
Male	6	8	14
TPO Antibodies			
Units: Subjects			
<35 IU/ml	12	16	28
≥35 IU/ml	12	8	20
Blood Pressure Systolic			
Units: mmHg			
median	154.5	155	
inter-quartile range (Q1-Q3)	140 to 176	142.5 to 166.5	-
Blood Pressure Diastolic			
Units: mmHg			
median	86.5	83	
inter-quartile range (Q1-Q3)	76 to 94	77 to 89	-
Height			

Units: cm			
arithmetic mean	159.2	158.4	
standard deviation	± 9.1	± 8.7	-
Weight			
Units: kg			
arithmetic mean	68.7	68.3	
standard deviation	± 13.2	± 13.3	-
BMI			
Units: kg/m2			
arithmetic mean	27.1	27.2	
standard deviation	± 4.8	± 4.6	-
Pulse			
Units: bpm			
arithmetic mean	67.8	68.1	
standard deviation	± 9.9	± 10	-
Blood Result TSH			
Units: mU/L			
median	1.05	2.05	
inter-quartile range (Q1-Q3)	0.76 to 1.69	1.12 to 2.75	-
Blood Result FT3			
Units: ppmol/L			
median	3.85	3.7	
inter-quartile range (Q1-Q3)	3.75 to 4.15	3.4 to 4.15	-
Blood Results FT4			
omitting patient 412 (usual dose arm) with FT4=36.0 pmol/L as this patient has a genetic condition whereby measured level of FT4 appears to be higher than it actually is			
Units: pmol/L			
median	18.8	18.75	
inter-quartile range (Q1-Q3)	17 to 20.2	16.55 to 19.35	-
Blood Results Total Cholesterol			
Units: mmol/L			
median	4.9	5	
inter-quartile range (Q1-Q3)	4.35 to 6.4	4.5 to 5.85	-
Blood Results HDL			
Units: mmol/L			
median	1.6	1.7	
inter-quartile range (Q1-Q3)	1.4 to 2	1.45 to 1.9	-
Blood Results Triglycerides			
Units: mmol/L			
median	1.35	1.25	
inter-quartile range (Q1-Q3)	1.05 to 2.2	1 to 1.8	-
Serum CTX			
Units: pg/mL			
median	0.25	0.32	
inter-quartile range (Q1-Q3)	0.18 to 0.34	0.14 to 0.47	-

End points

End points reporting groups

Reporting group title	Standard dose
Reporting group description:	
Participants will be randomised to usual dose LT4 (their current dose) to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group.	
Reporting group title	Reduced Dose
Reporting group description:	
Participants will be randomised to lower dose LT4 to be taken once daily. For participants randomised to lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1.	
Reporting group title	Standard Dose
Reporting group description:	
Participants will be randomised to usual dose LT4 (their current dose) to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group.	
Reporting group title	Reduced Dose
Reporting group description:	
Participants will be randomised to lower dose LT4 to be taken once daily. For participants randomised to the lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1.	

Primary: Participants' acceptability of study design

End point title	Participants' acceptability of study design[1]
End point description:	
as measured by the completion rate of participants in each randomised group	
End point type	Primary
End point timeframe:	
Baseline and follow up	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study and therefore is not powered to perform inferential statistical analysis

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: percentage				
number (not applicable)	87.5	79.2		

Statistical analyses

No statistical analyses for this end point

Primary: Dose Titration Strategy ITT

End point title	Dose Titration Strategy ITT[2]

End point description:

Dose titration strategy:

End point type	Primary

End point timeframe:

follow up

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study and therefore is not powered to perform inferential statistical analysis

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: percent				
number (not applicable)				
Percent achieving target TSH range at week 12 (vi	75	25		
Percent achieving target TSH range at week 24 (vi	79.2	41.7		

Statistical analyses

No statistical analyses for this end point

Primary: Dose titration strategy: Completers

End point title	Dose titration strategy: Completers[3]

End point description:

Dose titration strategy: Completers

End point type	Primary

End point timeframe:

follow up

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study and therefore is not powered to perform inferential statistical analysis

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: percent				
number (not applicable)				
Percent achieving target TSH range at week 12 (vi	85.7	31.6		
Percent achieving target TSH range at week 24 (vi	90.5	52.6		

Statistical analyses

No statistical analyses for this end point

Primary: Compliance (based on tablet count): ITT

End point title	Compliance (based on tablet count): ITT[4]

End point description:

Compliance (based on tablet count): ITT

End point type	Primary

End point timeframe:

follow up

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a feasibility study and therefore is not powered to perform inferential statistical analysis

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: percent				
number (not applicable)				
week 12 (visit 2)	87.5	79.2		
week 24 (visit 3)	87.5	75		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline ThyDQoL (qu. II)

End point title	Mean change from baseline ThyDQoL (qu. II)

End point description:

End point type	Secondary

End point timeframe:

follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score				
arithmetic mean (standard deviation)	-0.44 (± 0.78)	-0.47 (± 1.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline ThyDQol (AWI-18)

End point title	Mean change from baseline ThyDQol (AWI-18)

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score				
arithmetic mean (standard deviation)	-0.95 (± 1.67)	-0.17 (± 1.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline EQ-5D (VAS)

End point title	Mean change from baseline EQ-5D (VAS)

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score				
arithmetic mean (standard deviation)	4.9 (± 13.4)	-1.1 (± 10.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline Falls Risk Assessment Test score

End point title	Mean change from baseline Falls Risk Assessment Test score

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score				
arithmetic mean (standard deviation)	0.8 (± 2.2)	0 (± 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline TUG (time in seconds)

End point title	Mean change from baseline TUG (time in seconds)

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score				
arithmetic mean (standard deviation)	0.1 (± 3.1)	-0.2 (± 3.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline Total Cholesterol

End point title	Mean change from baseline Total Cholesterol

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.17 (± 0.49)	0.08 (± 0.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline HDL

End point title	Mean change from baseline HDL

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: mmol/L				
arithmetic mean (standard deviation)	0.05 (± 0.24)	0.06 (± 0.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline Triglycerides

End point title	Mean change from baseline Triglycerides

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.24 (± 0.55)	0.06 (± 0.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline Systolic Blood Pressure

End point title	Mean change from baseline Systolic Blood Pressure

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: mmHg				
arithmetic mean (standard deviation)	-16 (± 22.5)	-7 (± 27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline blood pressure diastolic

End point title	Mean change from baseline blood pressure diastolic

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: mmHg				
arithmetic mean (standard deviation)	-5.3 (± 9.28)	-3.3 (± 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline Weight

End point title	Mean change from baseline Weight

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: kg				
arithmetic mean (standard deviation)	-0.1 (± 1.76)	0.9 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline serum type 1 telopeptide

End point title	Mean change from baseline serum type 1 telopeptide

End point description:

End point type	Secondary

End point timeframe:
follow up

End point values	Standard Dose	Reduced Dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score				
arithmetic mean (standard deviation)	0.02 (± 0.16)	-0.08 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Underactive Thyroid Symptom Rating Questionnaire (ThySRQ)

End point title	Underactive Thyroid Symptom Rating Questionnaire (ThySRQ)

End point description:
Have you felt tired in recent weeks?, percentage tired.

End point type	Secondary

End point timeframe:
baseline and follow up

End point values	Standard Dose	Standard dose	Reduced Dose	Reduced Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	21	19	19
Units: percentage				
number (not applicable)	81	95	78	83

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During Follow Up	
Adverse event reporting additional description:	
Adverse events were reported at wk 24	
Assessment type	Systematic

Dictionary used	
Dictionary name	As Reported
Dictionary version	n/a

Reporting groups	
Reporting group title	Standard dose
Reporting group description:	
Participants will be randomised to usual dose LT4 (their current dose) to be taken once daily. For participants randomised to usual dose and who have a TSH level between 4.1 – 4.7 at the screening visit, their dose of LT4 will be increased by 25mcgs daily so that they are within the desired TSH range for this group.	
Reporting group title	Reduced Dose
Reporting group description:	
Participants will be randomised to lower dose LT4 to be taken once daily. For participants randomised to lower dose LT4 (target TSH levels 4.1 – 8.0 mU/L), participants in the lower dose LT4 arm are likely to have their LT4 medication reduced by 25mcgs once a day at visit 1.	

Serious adverse events	Standard dose	Reduced Dose	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Overdose on levothyroxine			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Mild Stroke			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
VF arrest due to acute myocardial infarction			

subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Standard dose	Reduced Dose	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 24 (66.67%)	21 / 24 (87.50%)	
General disorders and administration site conditions			
Balance Problems			
subjects affected / exposed	4 / 24 (16.67%)	4 / 24 (16.67%)	
occurrences (all)	4	4	
Brittle Nails			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Dizzy			
subjects affected / exposed	2 / 24 (8.33%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Dry Hair			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Memory Problems			
subjects affected / exposed	0 / 24 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Slow			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Tired			
subjects affected / exposed	9 / 24 (37.50%)	14 / 24 (58.33%)	
occurrences (all)	9	14	
Weight Gain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	0	
Chest Pain			

subjects affected / exposed	0 / 24 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Feeling Unwell			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Sore Throat			
subjects affected / exposed	0 / 24 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	0	
Cold sweat			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	0	
Confusional state			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Raised Temperature			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Hayfever			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Heat Intolerance			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Lack of motivation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Restless leg			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Hypertension			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Immune system disorders			
Common Cold			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Left Ear blocked and bleeding			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 24 (4.17%)	4 / 24 (16.67%)	
occurrences (all)	1	4	
Loss of appetite			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Abdominal colic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Loose Stools			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal			

disorders			
Breathless			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Palpatations			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Shortness of Breath			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry Skin			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Bruised Face			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin discolouration (breast)			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Skin Lesions			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
swollen top half of face, itchy blotches			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depressed			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Stress			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
Brown urine			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Incontinence			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Kidney dysfunction			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Joint Pain			
subjects affected / exposed	2 / 24 (8.33%)	3 / 24 (12.50%)	
occurrences (all)	3	3	
Muscle Ache			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Swollen Ankes			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Bilateral ankle oedema			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	0	
Gout			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Left Leg/Ankle Swollen			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Numbness in hands and legs			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
oedematous right foot			

subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Osteoarthritis flare up			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pain in neck			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infected Right Foot			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Vaginal Thrush			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2012	- The addition of the ISRCTN number and the Clinicaltrials.gov Number, as this study been registered for both since the approval of the last protocol. - The Trial Manager's details have been amended from Dr Catherine Watson to Ms Melinda Jeffels, due to a change in study management. - The protocol version number and date has been updated to ensure version control is kept. - The abbreviation of RfPB (Research for Patient Benefit) has been added to the abbreviation section of the protocol. - The name of the manufacturer of Eltroxin to be used in this study was changed from Goldsheild Group Limited to Mercury Pharma Group Limited, due to a change in the name of the Manufacturer (it should be noted that the marketing authorization of the product PL number remains unchanged) - The web address details for the online randomization system, as well as the availability details, have been added to the protocol as they have now been confirmed. - The SAE fax and telephone numbers have been added to the protocol as these have been confirmed as well.
29 April 2013	- The inclusion criteria regarding required TSH levels to be eligible for the study (originally 0.4 – 4 mU/L) has been amended in order to reflect the local laboratory reference ranges (0.3 – 4.7 mU/L) in order to ensure that all patients with normal TSH levels can be enrolled on the study. - The protocol version number and date has been updated to ensure version control is kept.
14 June 2013	Update the status of Newcastle PCT to a site from a PIC.
30 October 2013	Due to the limited availability of trial IMP Eltroxin. Current stock of Eltroxin expires on the 14th of November, so we request the flexibility to use the generic medication Levothyroxine instead.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

none

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23522096